REMARKS

Applicants have amended Claim 4 to correct a grammatical error. Claim 19 is amended to recite that the claimed host cell is isolated. Support for this amendment can be found, for example, at paragraph [0291] through [0296] of the specification and in the claims as originally filed. Claims 4-6, 11-14 and 16-31 are presented for examination. No new matter is added by the amendments.

Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed June 14, 2005. For the reasons set forth below, Applicants respectfully traverse.

Priority Determination:

The PTO has stated that because the claims do not meet the requirements of 35 U.S.C. § 112, first paragraph, Applicants are not entitled to the benefit of priority to any earlier filed application. However, for the reasons set forth below, the instant application and the priority applications do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date.

The sequences of SEQ ID NO:77 and 78 were first disclosed in US Provisional Application 60/099,741 filed 9/10/1998 as SEQ ID NO:1 and 2 and in Figures 1 and 2. These same sequences were disclosed in PCT/US99/20111 and in 09/403,297 as SEQ ID NO:127 and 128, Figures 71 and 72. The data in Example 18 (Tumor Versus Normal Differential Tissue Expression Distribution), relied on in part for the utility of the claimed nucleic acids, were first disclosed in PCT Application PCT/US00/23328 filed 8/24/2000, on page 93, line 3, through page 96, line 35. Thus, Applicants maintain that the present application is fully entitled to the benefit of at least the priority date of August 24, 2000.

Rejection under 35 U.S.C. § 112, second paragraph

The PTO rejected Claims 14-16 and 21-25 under 35 U.S.C. § 112, second paragraph, as being indefinite. The PTO states that it is unclear what range is intended by the phrase "at least about."

Applicants submit that recitation of "at least about" is clear and definite in view of Applicants' specification. For example, the specification, at paragraph [0012] states that "about" can mean the recited nucleotide sequence length plus or minus 10% of the recited length. In

view of the teachings of the specification, Applicants respectfully request removal of this rejection of the claims.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO rejected Claims 4-6, 11-14 and 16-31 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The PTO argues that undue experimentation would be required to use the claimed nucleic acids.

Applicants respectfully traverse.

Applicants submit that one skilled in the art could have made and used the claimed nucleic acids without undue experimentation. The PTO evaluates the invention in the light of factors to be considered for enablement (herein referred to as "Wands factors") in asserting that the claimed nucleic acids cannot be used without undue experimentation. The PTO does not appear to assert that the claimed nucleic acids cannot be made. Accordingly, Applicants address only whether or not one skilled in the art could have used the claimed nucleic acids without undue experimentation.

The PTO considers several Wands factors in concluding that the claimed nucleic acids lack enablement. Regarding the nature of the invention, the state of the prior art, and the skill in the art, the PTO acknowledges that nucleic acids could be used as tumor markers and screening methods were known, but the PTO asserts that no nucleic acids similar to SEQ ID NO:77 had been identified in the art, and that interpretation of differential screening methods depended on differences in levels, the ability to generalize and reproduce results, and the ability to pinpoint tumor type. The PTO also asserts that it was not routine in the art to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid. Regarding the specification, the PTO states that there are no working examples and little guidance provided for using the claimed nucleic acids. The PTO states that the specification fails to disclose the specific type of tumor, level of expression, relative amounts, and how many different cDNA libraries were screened. Regarding the breadth of the claims, the PTO concludes that the claims are broad. Based on these considerations, the PTO determines that it would have required undue experimentation to use the claimed nucleic acids.

Applicants respectfully submit that, one skilled in the art, in view of the teachings of the specification, could have readily used the claimed nucleic acids.

Regarding the state of and level of skill in the art, Applicants submit that one skilled in the art knew how to use nucleic acids, such as the claimed nucleic acids, in hybridization studies. As acknowledged by the PTO, nucleic acid methods such as differential screening methods have been routine for more than a decade. Further, it is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, it unquestionable that one skilled in the art knew how to use a nucleic acid such as the recited nucleic acids in nucleic acid methods such as hybridization assays of samples.

Regarding the PTO's assertion that "it was not routine to use as a tumor probe a nucleic acid less than 100% identical to the target nucleic acid" (Office Action at 4), this assertion represents official notice without documentary evidence. Since the routine percent identity of a probe to its target is not common knowledge or well-known, Applicants request documentary evidence in support of the noticed fact, in accordance with *In re Zurko*, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001).

Regarding the teachings of the specification, Applicants submit that specific guidance and a working example are provided in Applicants' disclosure. The specification, for example, at paragraphs [0311] and [0449]-[0452] (Example 5), teaches various methods for using the claimed nucleic acids, for example, in hybridization assays of samples. The specification also provides a working example, Example 18 (paragraph [0530]), in which differential expression experiments are described, and the results of the experiments revealed that in stomach and lung, the nucleic acid encoding PRO1357 was underexpressed for tumor relative to normal. Furthermore, the PTO has recognized the fact that the claimed nucleic acids are useful as tumor markers, stating "the asserted utility for the nucleic acid as a tumor marker for stomach and lung tumor is accepted." Office Action at 3. Accordingly, the PTO recognizes that the claimed nucleic acids are useful as tumor markers, and the specification provides specific teachings and a working example of methods and specific organs to target in tumor detection methods.

In sum, nucleic acid methods such as hybridization methods are routine, as acknowledged by the PTO. The claimed nucleic acids have utility as tumor markers, as acknowledged by the PTO. The specification provides guidance on methods for using the claimed nucleic acids. The

specification also provides a working example identifying particular organs to target in using the claimed nucleic acids. Since it was routine in the art to use nucleic acids in, for example, hybridization methods of nucleic acid detection, one skilled in the art would need no more than routine experimentation to use the claimed nucleic acids to detect PRO1357 nucleic acids in stomach and lung samples.

The PTO indicates that the specification is insufficient because the specific type of tumor is not disclosed, nor are levels of expression, relative amounts or how many different tumor cDNA libraries from each tumor tissue were screened. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. MPEP §2164.01; *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Based on the teachings of the specification and the level of skill in the art, it was routine to use nucleic acids such as the claimed nucleic acids in hybridization assays, differential expression in tumor versus normal tissue was established, and one skilled in the art knew which particular organs to target for detection with the nucleic acids. No undue experimentation was required for a Ph.D. scientist with several years of experience to use these routine methods, in view of the teachings in the specification, in order to determine details such as the exact location of the PRO1357 nucleic acid or to determine specific details of differential expression between normal and tumor. Accordingly, it would not have required undue experimentation for one skilled in the art to make and use the claimed nucleic acids. The claimed invention is, therefore, fully enabled.

The PTO dismisses the Declaration by Grimaldi because it allegedly does not fill important gaps in the disclosure such as "expression level range for normal and tumor tissues, specific types of stomach or lung tumors detectable, and probability of detection for any particular stomach or lung tumor type." As discussed above, nucleic acid methods were routine in the art, and the need to test more than one sample in refining specific details of experimental parameters does not represent undue experimentation. The Grimaldi Declaration describes the assays conducted and explains the results of Example 18 were indicative of at least a two-fold

difference in expression between tumor and normal samples. This Declaration further underscores that it would have been no more than routine experimentation to use the claimed nucleic acids in methods such as, for example, the method of Example 18.

The PTO cites the publication by Hu et al. for the proposition that it is unclear if the expression changes in Example 18 are significant. The PTO quotes the portion of Hu stating:

> It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful.

As the PTO has asserted, Hu studied differential gene expression and a *known* role in a disease. Office Action mailed December 13, 2004, at 5. Thus, Hu's analysis of differential expression of a gene whose role in a disease is "biologically meaningful" to the disease is completely different from Applicants' asserted differential expression of a gene for diagnostic purposes. Even if a gene does not have a meaningful role in causing a disease, this does not indicate that the gene does not show a consistent and measurable change in expression in the cancer. Whether or not a differentially expressed gene has a biologically meaningful role in a disease does not change the fact that differential expression of a gene and encoded polypeptide can be used in diagnosis of a disease. The lack of a biologically meaningful role of PRO1357 in cancer, for example, is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO1357 is differentially expressed, or the biological meaning of the differential expression, in order to exploit the differential expression to distinguish tumor from normal tissue.

Further, as noted above, the utility of the PRO1357 nucleic acid is accepted by the PTO. Thus, insofar as the PTO is using Hu to challenge the utility of the claimed nucleic acids by questioning the validity of Applicants data regarding differential expression of the nucleic acid encoding the PRO1357 polypeptide, this point is now moot.

In view of the teachings in the specification and the knowledge in the art, Applicants submit that the claimed nucleic acids are fully enabled. This assertion is supported by the Declaration by Dr. Grimaldi. Further, the reference by Hu provides no basis to question the ability of one skilled in the art to use of the claimed nucleic acids. Accordingly, Applicants

respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of Claims 4, 5 and 17-20 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The PTO states that nucleic acids that are non-identical to SEQ ID NO:77 with the claimed expression pattern are not described. Applicants respectfully disagree.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The subject matter of the pending claims concerns nucleic acids having 95% or 99% sequence identity to the nucleic acid sequence of SEQ ID NO:77, the full-length coding sequence of the nucleic acid sequence of SEQ ID NO:77, or the full-length coding sequence of the cDNA deposited under ATCC accession number 203240, with the functional recitation: "wherein said isolated nucleic acid is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor, respectively."

Applicants submit that the pending claims relating to nucleic acids having 95% or 99% sequence identity to the nucleic acids related to SEQ ID NO:77 with the functional recitation "wherein said isolated nucleic acid is more highly expressed in normal stomach tissue or normal lung tissue compared to stomach tumor or lung tumor, respectively" are adequately described. In Example 14 of the written description training materials, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors. In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make nucleic acids which have at least 95% sequence identity to the disclosed sequences, and the specification discloses how to test to determine if the sequence is differentially expressed in lung or stomach tumors. Like Example 14, the genus of nucleic acids that have at least 95% or 99% sequence identity to the disclosed sequences will not have substantial variation since all of the variants must have the same expression in certain tumors.

Furthermore, while Applicants appreciate that actions taken by the PTO in other applications are not binding with respect to the examination of the present application, Applicants note that the PTO has issued many patents containing claims to variant nucleic acids or variant proteins where the applicants did not actually make such nucleic acids or proteins. Representative patents include U.S. Patent No. 6,737,522, U.S. Patent No. 6,395,306, U.S. Patent No. 6,025,156, U.S. Patent No. 6,645,499, U.S. Patent No. 6,498,235, and U.S. Patent No. 6,730,502, which were submitted as exhibits in Applicants' previous response.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO: 77,

by reciting in the claims identity 95% or 99% identity to fully described nucleic acids, and by describing in the specification the gene expression assay, which results in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §102(b) – Anticipation

Claims 4-6, 11-14 and 16-31 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO 01/16318, WO 00/12708, and GenBank Accession BG529820.

The data in Example 18 were disclosed in priority application, PCT/US00/23328 filed August 24, 2000, which is the PCT application published as WO 01/16318. As discussed above, the instant application and the priority applications do meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore, are entitled to an earlier priority date. Therefore, the present claims are entitled to at least the priority date of August 24, 2000. Accordingly, WO 01/16318 is not prior art under § 102(b).

WO 00/12708 was published on March 9, 2000, which is less than one year before the filing of priority application PCT/US00/23328 (August 24, 2000). Again, PCT/US00/23328 discloses the differential expression data which, among other disclosures, meets the requirements of 35 U.S.C. § 112, first paragraph, and therefore, entitles Applicants to at least the priority date of August 24, 2000. Therefore, WO 00/12708 is not prior art under § 102(b).

GenBank Accession BG529820 was made available on April 3, 2001, which is subsequent to the filing of priority application PCT/US00/23328 (August 24, 2000). Because, PCT/US00/23328 meets the requirements of 35 U.S.C. § 112, first paragraph, Applicants are entitled to at least the priority date of August 24, 2000. Therefore, GenBank Accession BG529820 is not prior art under § 102(b).

In view of the above discussion, reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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